for Applicants pointed out that the pending claims are not rendered obvious by the cited references, alone or in combination, since the cited references did not provide a reasonable expectation of success in achieving the claimed methods. As evidence in support of this position, a Declaration under 37 C.F.R. § 1.132 of Dr. Peter Beetham was submitted, in which Dr. Beetham stated his opinion, and belief that a scientist knowledgeable in the field of plant molecular biology and plant transformation would also hold the opinion, that the cited prior art references do not provide the required reasonable expectation of success in achieving the claimed methods because it could not have been reasonably predicted that the recombinagenic oligonucleobases could be successfully adhered to the biolistics particle and resolubilized off the particle once in the plant cell, and that it could not have been reasonably predicted that the required secondary structure of the oligonucleobase molecule would be maintained throughout the biolistics method for successfully making a desired localized mutation in a target gene.

Attorneys for Applicants now invite the Examiner's attention to the Declaration under 37 C.F.R. § 1.132 of Dr. Richard A. Metz ("the Metz Declaration") submitted herewith, which sets forth additional evidence supporting the conclusion that the prior art does not provide a reasonable expectation of success in achieving the claimed invention.

Dr. Metz holds a Ph.D. and has post-doctoral experience. Dr. Metz is at least a person of ordinary skill in the art. Dr. Metz states his familiarity with the application and the relevant rejection. See Paragraphs 2-4 of the Metz Declaration. Dr. Metz explains in Paragraph 5 of his Declaration that he is a scientific investigator and manager of technical research and development, that his professional research interests have focused upon a number of areas including gene therapy, homologous recombination, DNA repair and gene targeting in microbial systems, and that he has been involved in gene therapy, site-directed mutagenesis, and more recently commercial applications of recombinagenic nucleobases. Moreover, in Paragraph 6 of the Metz Declaration, Dr. Metz explains that his research experience also includes the use of biolistics technology, and that more than one thousand uses of recombinagenic oligonucleobases and more than fifty uses of biolistics technology in microbial systems have been performed either by Dr. Metz personally or under his supervision and control.

Dr. Metz explains in Paragraph 7 that the biolistics technology requires the nucleic acid molecules be precipitated onto microparticle projectiles, usually a suspension of gold particles one micron in diameter, in a harsh solution of salts, *e.g.*, calcium chloride, and positively charged proteins, *e.g.*, spermadine. The nucleic acid-coated particles are then literally "shot" into cells. Dr. Metz states that the recombinagenic oligonucleobases of the present invention are radically different in size and structure than the nucleic acid molecules that were typically employed and known to work in biolistics technology applications at the time the present invention was made. Metz Declaration, ¶ 8. Dr. Metz explains that the recombinagenic oligonucleobases of the present invention are small single-chained molecules with short regions of secondary structure, which secondary structure is fragile because of its limited length but is critical for maintaining functionality of the molecule. *Id.* Dr. Metz further states that based on experiments performed in the laboratories of ValiGen (US), Inc., it is known that the measurable activity of the recombinagenic oligonucleobases is lost if the recombinagenic oligonucleobases are repeatedly frozen and thawed in an aqueous solution. *Id.* Further, the oligonucleobases also lose activity over time when maintained at 4°C in an aqueous solution, and under some circumstances losing all measurable activity after being stored for a couple of weeks. *Id.* Dr. Metz explains that it is believed that the loss in activity is due to the loss of required secondary structure since renaturation of the oligonucleobase molecule results in a restoration of activity. *Id.* Dr. Metz further states that the loss of secondary structure is not a problem with most transformation systems since recombinagenic oligonucleobases can be renatured before use, even after following exposure to conditions that would destroy any secondary structure or favor inactive secondary structure or concatamer formation. *Id.* Dr. Metz continues:

> However, after adherence of the recombinagenic oligonucleobases to a particle in accordance with biolistics technology described in U.S. Patent No. 5,204,253 and in the present specification, the option of renaturing the oligonucleobase molecules is not available since that might result in stripping the oligonucleobase molecules from the particle.

Metz Declaration, ¶ 9.

Dr. Metz states that it is his opinion, and believes that a scientist knowledgeable in the field of chimeraplasty and molecular biology of human and microbial systems would also hold the opinion, that the cited prior art references do not provide the required reasonable expectation of success in achieving the claimed methods because it could not have been reasonably predicted that the short regions of secondary structure of the

recombinagenic oligonucleobases would survive the harsh conditions under which the oligonucleobases are precipitated onto the gold particle, *i.e.*, it could not be reasonably predicted that the secondary structure required for activity of the oligonucleobase molecules would be maintained. Metz Declaration, ¶ 9.

Based on his research experience and the foregoing, Dr. Metz concludes, and believes that a scientist knowledgeable in the field of chimeraplasty and molecular biology of human and microbial systems would also conclude, that the teachings of U.S. Patent Nos. 5,565,350; 5,731,181; and 5,204,253, either alone or in combination, do not render obvious methods of making a localized mutation causing a desired trait in a target gene in a plant cell comprising adhering to a particle a recombinagenic oligonucleobase, introducing the particle into a cell of a population of plant cells and identifying a cell of the population having a mutation, or comprising perforating the cell walls of a population of plant cells, introducing a recombinagenic oligonucleobase and identifying a cell of the population having a mutation, because the prior art does not provide a reasonable expectation of success in achieving such methods since recombinagenic oligonucleobases are sufficiently different from the double-stranded and single-stranded nucleic acid molecules employed in prior art biolistics methods in that the molecules have regions of secondary structure which are required for activity. Metz Declaration, ¶ 10. Accordingly, Dr. Metz concludes, and believes a scientist knowledgeable in the field of molecular biology of human and microbial systems would also conclude, that the claimed methods of the present invention are nonobvious in view of the cited prior art.

The legal standard for a rejection of claimed subject matter as obvious in view of a combination of prior art references is that (1) the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or use the claimed method, as the case may be, and (2) the prior art must have revealed that in so doing, those of ordinary skill would have had a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Attorneys for Applicants point out that based on the foregoing discussion and the Declaration of Dr. Metz, the prior art did not and could not reveal to those of ordinary skill in the art that they would have had a reasonable expectation of success in achieving the claimed invention. In other words, the prior art did not provide a reasonable expectation of success that the particle bombardment method of

Sanford would allow for the successful making of a localized mutation in a desired gene in a plant cell using the recombinagenic oligonucleobases described by Kmiec I and II.

In view of the foregoing discussion, and the discussion in the Reply under 37 C.F.R. § 1.111 filed on June 6, 2001, Attorneys for Applicants submit that the rejection under Section 103 is in error, and respectfully request withdrawal of the Section 103 rejection.

CONCLUSION

Attorneys for Applicants respectfully request that the remarks of the present response be made of record in the present application. Claims 1-4 and 8-27 fully meet all statutory requirements for patentability. Withdrawal of the Examiner's rejections is respectfully requested.

Attorneys for Applicants respectfully request that the Examiner call the undersigned at (212) 790-9090 if any questions or issues remain.

Respectfully submitted,

Date: June 28, 2001

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Enclosure